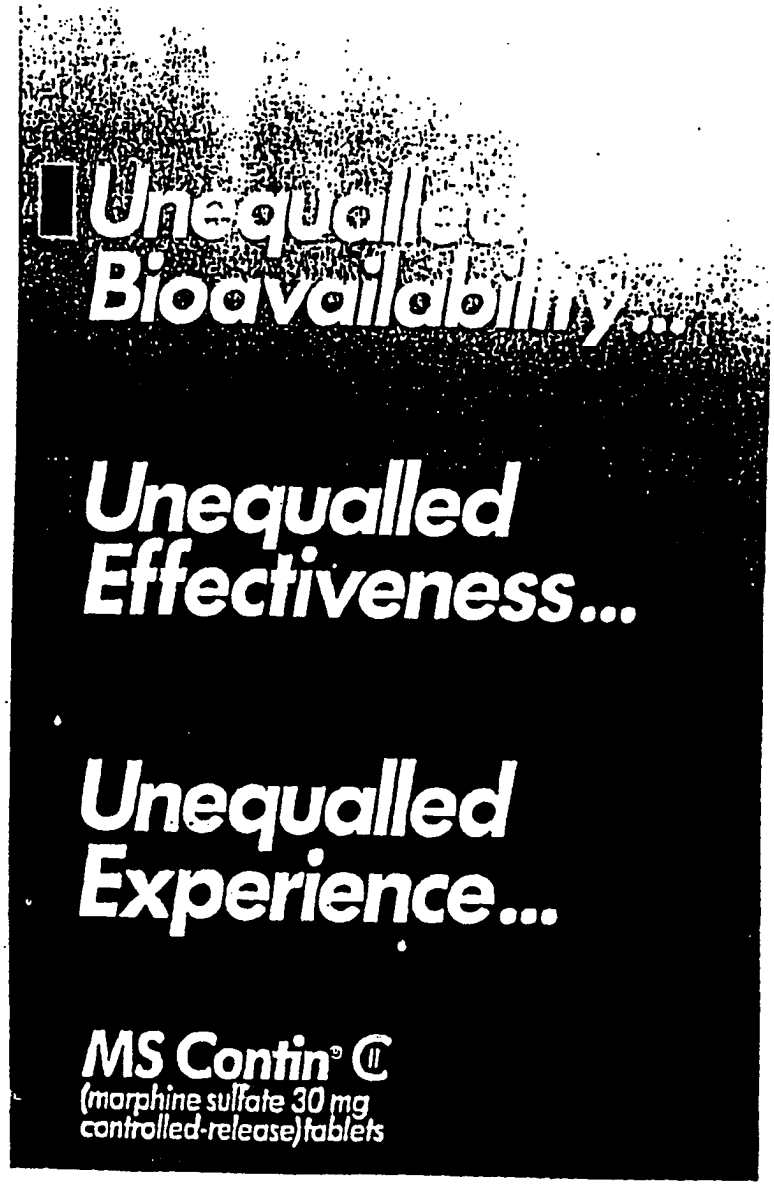
BS

MS Contin is Unequalled...



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6/19/02 GCB

Unequalled Bioavailability...

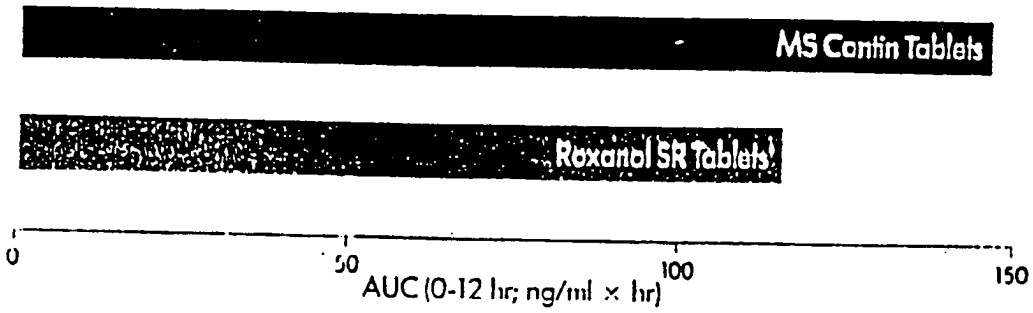
MS Contin has superior 12-hour bioavailability:

MS Contin is 27% more bioavailable than Roxanol SR.

Bioavailability:
"The extent to which a drug reaches its site of action or a biological fluid from which the drug has access to its site of action."

[illegible]

Bioavailability (0-12 hr) of MS Contin 30 mg Tablets vs. Roxanol SR 30 mg Tablets as determined by plasma drug levels in a crossover study in 18 normal volunteers†



Important Note: While there is an indirect relationship between plasma morphine levels and analgesia, higher plasma levels are generally associated with superior relief of pain, as demonstrated in the literature. There is a lag time or hysteresis between the time of peak plasma morphine levels and the time of peak drug effects."

[illegible]

12-Hour MS Contin...

MS Contin® (morphine sulfate 30 mg controlled-release) tablets C II

- *No other morphine product is bioequivalent to MS Contin.*
- *MS Contin and Roxanol SR are not bioequivalent, therefore, Roxanol SR is not therapeutically interchangeable with MS Contin.*[1,11]
- *MS Contin reaches a significantly higher peak concentration, for more effective analgesia.*

Bioequivalence:
"They [pharmaceutical formulations] are said to be biologically equivalent if they yield similar concentrations of drug in blood and tissues...Pharmaceutical preparations that are chemically equivalent but not biologically or therapeutically equivalent are said to differ in their bioavailability."

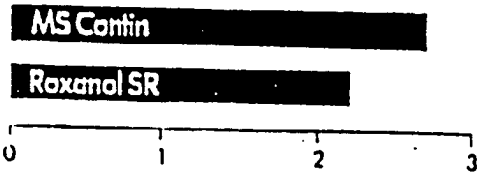
The three criteria for bioequivalency are comparable...

1. bioavailability (calculated from area under the time-concentration-curve)
2. time to peak plasma concentration
3. peak concentration

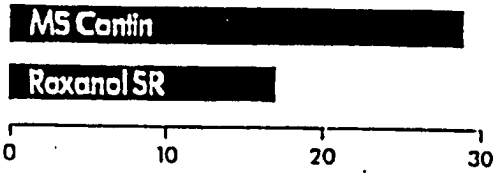
Results of Comparative Study[1]

	MS Contin (2 × 30 mg)	Roxanol SR (2 × 30 mg)
AUC	147 (0-12 hr; ng/ml × hr)	116
T_{max} (hrs)	2.7	2.2
C_{max} (ng/ml)	29	17

Time to Peak Concentration (T_{max})[1]



Peak Concentration (C_{max})[1]



[1] and [11] are Comparative Bioavailability of Two Controlled-Release Oral Morphine Tablets, Accepted for presentation at the Sixth Annual Meeting of the American Pain Society, Washington, DC, Nov. 1990 and Comparative Pharmacokinetics of Controlled-Release Oral Morphine Tablets for Eight vs Twelve Hour Analgesia. Accepted for presentation at the 6th World Conference on Clinical Pharmacology and Therapeutics, Stockholm, Sweden, August 1989.

Proven Against Cancer Pain

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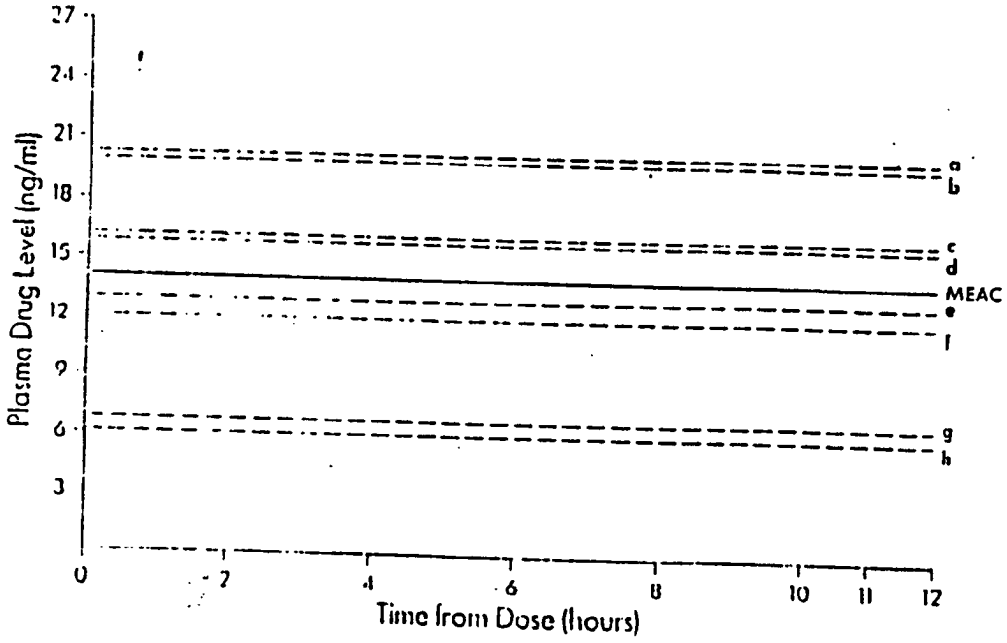
Unequalled Effectiveness...

What is the effective analgesic level of oral morphine?

A careful review of the literature[a-h] indicates the complexity of defining effective analgesic plasma morphine levels. However, there is generally a "Minimally Effective Analgesic Concentration" (MEAC) of plasma morphine below which no analgesia is provided (see Chart below).

Minimally Effective Analgesic Concentrations (MEAC) of Morphine

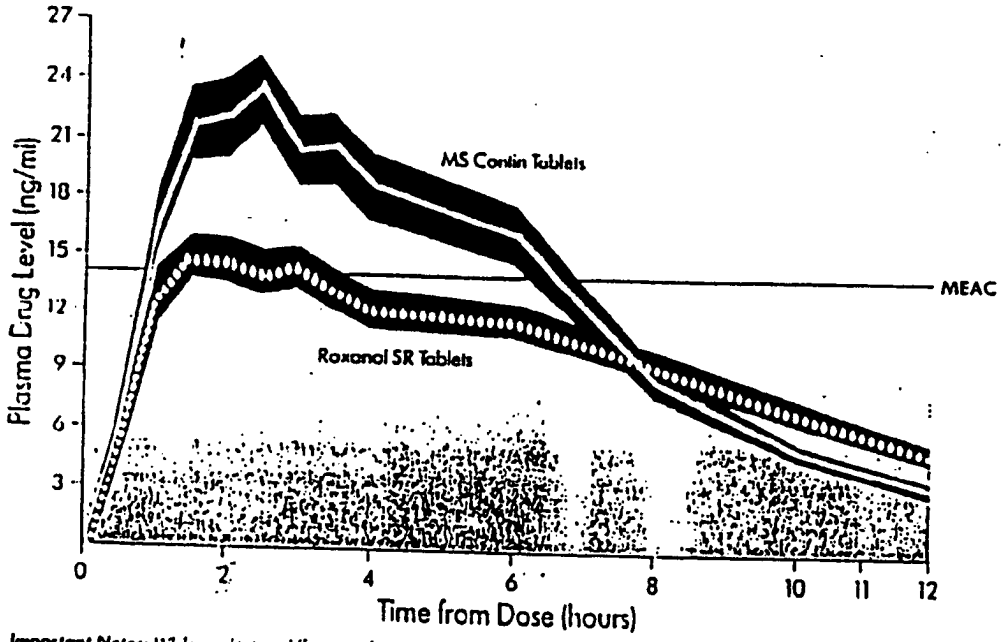


12-Hour MS Contin[®]...

MS Contin® (morphine sulfate 30 mg controlled-release) tablets C II

- MS Contin achieves significantly higher analgesic concentrations.[1,11]
- MS Contin maintains plasma levels above the minimally effective analgesic concentration (MEAC) significantly longer.

Plasma morphine concentration (mean ± SE) following equal doses of MS Contin and Roxanol SR†



Important Note: Wide qualitative differences between morphine formulations are unlikely to vary among subject groups, the absolute magnitude of plasma morphine levels and pharmacokinetic parameters observed here in young normal subjects are likely to be different from those in older subjects and in patients with advanced disease. For example, the apparent plasma morphine elimination half-life can be expected to be prolonged in such patients.

Additionally, there is a lag time, or hysteresis, between the time of peak plasma morphine levels and the time of peak drug effects.[11]

Proven Against Cancer Pain

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Unequalled Experience...

- Extensive published clinical documentation that supports 12-hour efficacy and safety[1-14]
- Over 6 years' proven clinical experience with over a half-million prescriptions[1]
- MS Contin has a clinically documented safety profile:
  In over 95% of patients, side effects were fewer or equal to pre-study analgesic[15-17]

Percent of patients experiencing fewer or equal side effects[15-17]

Study #1: Memorial Sloan-Kettering Cancer Center

55% of patients experienced fewer side effects
21% of patients experienced equal side effects

Study #2: New York University School of Medicine

94% of patients experienced fewer side effects
6% of patients experienced equal side effects

Study #3: Bowman Gray School of Medicine

52% of patients experienced fewer side effects
48% of patients experienced equal side effects

12-Hour MS Contin...

MS Contin® (morphine sulfate 30 mg controlled-release) tablets Ⓒ II

- *MS Contin is the subject of two international symposia on pain control.*[18-19]
- *Safety and efficacy demonstrated at prestigious cancer treatment centers in over 1200 study patients.*
- *Professional educational support:*
  Speakers' Bureau; Educational Slides and Videotapes, including "Cancer Pain Management" Chaired by Dr. Kathleen M. Foley of Memorial Sloan-Kettering Cancer Center.
- *MS Contin Tablets are small, round and film coated.*
  Their distinctive lavender color makes them easy to recognize and identify. Their small size (less than half that of Roxanol SR) makes them easy to swallow.

[illegible]

Proven Against Cancer Pain

MS Contin® is Unequalled...

The only 12-hour oral narcotic analgesic proven against cancer pain.

- Superior 12-hour bioavailability – 27% more bioavailable than Roxanol SR.
- No other morphine product is bioequivalent to MS Contin; therefore, none is therapeutically interchangeable.
- Achieves a significantly higher peak concentration – for more effective analgesia.
- Maintains plasma morphine levels above the minimally effective analgesic concentration (MEAC) significantly longer – for effective pain relief.
- Published clinical documentation of superior or equal efficacy compared to immediate-release morphine and other oral opioid analgesics.
- Proven safety profile – published clinical documentation shows fewer side effects than previous analgesic (Hydromorphone, Methadone, Oxycodone, Codeine, Meperidine).

Also available

MSIR® Useful in starting patients on morphine or for treating breakthrough or incident pain.

(morphine sulfate) 15 mg and 30 mg Immediate-Release tablets C II

12-hour MS Contin® C II

(morphine sulfate 30 mg controlled-release) tablets

Proven Against Cancer Pain

For Prescribing Information Please See Accompanying Professional Literature

Purdue Frederick 8214J PM28

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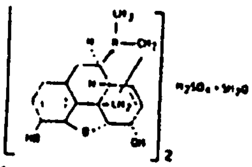
MS CONTIN® 30 mg Tablets
MS CONTIN® 60 mg Tablets
MS CONTIN® 100 mg Tablets
Morphine Sulfate Controlled-Release (CII)

WARNING: May be habit forming.

E2220

DESCRIPTION:

Chemically, morphine sulfate is 7,8-didehydro-4,5α-epoxy-17-methylmorphinan-3,6α-diol sulfate (2:1) (salt) pentahydrate and has the following structural formula



Each MS CONTIN 15 mg Controlled Release Tablet contains: 15 mg Morphine Sulfate U.S.P. Inactive ingredients: Cetostearyl Alcohol, FD&C Blue No. 2, Hydroxyethyl Cellulose, Hydroxypropyl Methylcellulose, Lactose, Magnesium Stearate, Talc, Titanium Dioxide and other ingredients.

Each MS CONTIN 30 mg Controlled Release Tablet contains: 30 mg Morphine Sulfate U.S.P. Inactive ingredients: Cetostearyl Alcohol, D&C Red No. 7, FD&C Blue No. 1, ...

CLINICAL PHARMACOLOGY:

PHARMACODYNAMICS:

INDICATIONS AND USAGE:

CONTRAINDICATIONS:

WARNINGS: (See also: CLINICAL PHARMACOLOGY)

PRECAUTIONS: (See also: CLINICAL PHARMACOLOGY)

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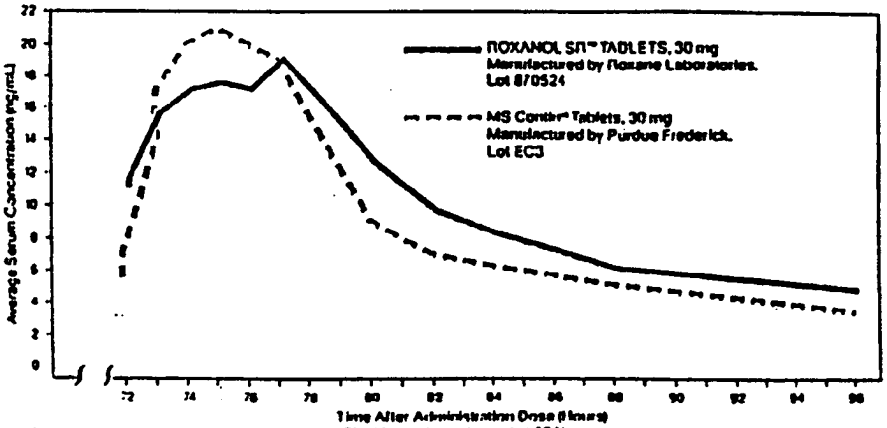
AVERAGE SERUM CONCENTRATIONS OF
MORPHINE FOR ROXANOL SR™ TABLETS AND MS CONTIN® TABLETS
Steady State (Multiple Dose) Study (30 mg every 12 hours x 7 doses)



Adapted from Abstracts of the 1988 American Society of Clinical Oncologists Meeting

Multiple-dose randomized crossover trial demonstrates Roxanol SR and MS Contin are bioequivalent.

☐ Evaluations of standard pharmacokinetic parameters (AUC 79-96 hr, AUC 72-84 hr, Cmax and Cavg) showed less than 10% difference between the two sustained release morphine treatments.

☐ The investigators concluded that Roxanol SR is bioequivalent to MS Contin.

More cost-effective than MS Contin

☐ Roxanol SR offers greater cost containment benefits for hospitals.*

☐ Roxanol SR is a greater value for patients who need relief of chronic cancer pain.*

*[illegible]

ROXANOL SR™ Tablets 30 mg

(Morphine Sulfate Sustained Release Tablets)

WARNING: May be habit forming.

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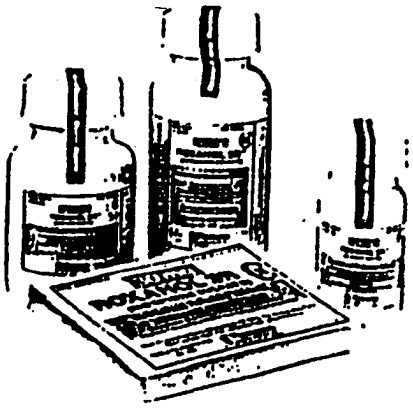
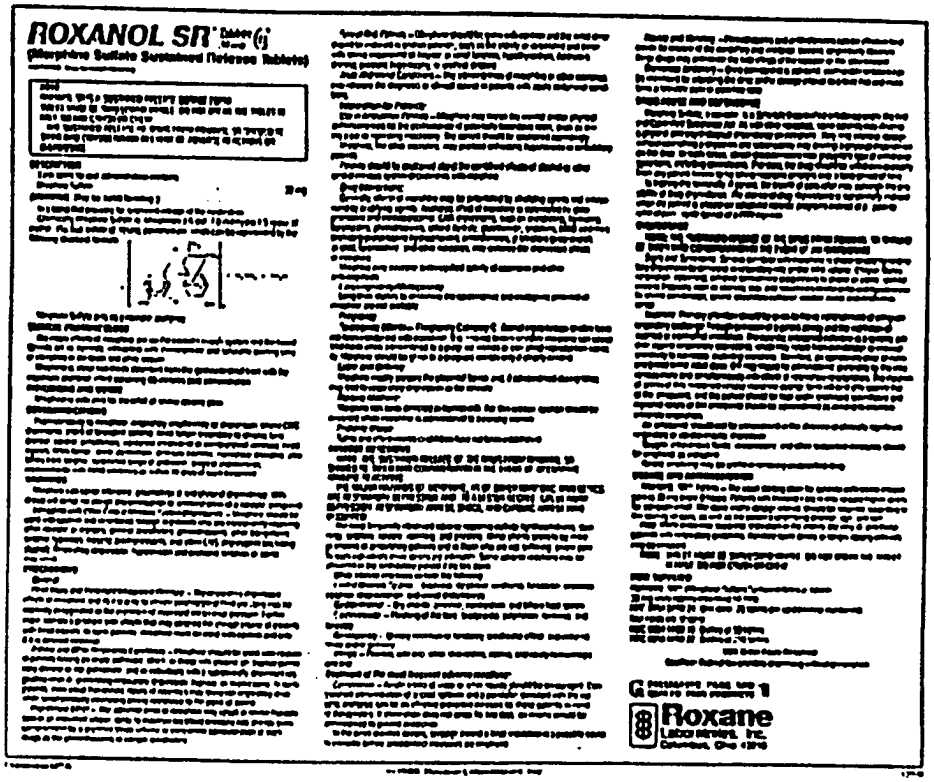
Dosing and Administration

The patients should first be stabilized on Roxanol Concentrated Oral Solution. Convert to Roxanol SR by dividing the total daily Roxanol requirement (in milligrams) by three and administering as Roxanol SR Tablets every eight hours. The dose and dosage schedule can be adjusted for greater flexibility according to severity of pain as well as for the patient's underlying disease, age, and size.

Tablets must be swallowed whole...not broken, crushed, or chewed. Tablets have a methyl cellulose coating for easier swallowing.





ROXANOL SR

Roxane